RNA NANOPARTICLES FOR BRAIN TUMOR TREATMENT

RELATED APPLICATIONS

[0001] This application is a Divisional Application of U.S. application Ser. No. 15/554,360, which issued as U.S. Pat. No. 10,584,144 on Mar. 10, 2020, which is a §371 National Stage Application of PCT/US2016/021447 filed Mar. 9, 2016, which claims the benefit of U.S. Provisional Patent Application No. 62/130,459, filed Mar. 9, 2015, the entire disclosures of which are hereby incorporated by reference in their entireties.

GOVERNMENT INTEREST

[0002] This invention was made with government support under CA151648 (P.G.), EB012135 (P.G.), CA152758 (C.M.C.), CA175875 (I.N.), CA163205 (I.N.), P30NS045758 (B.K.), R01064607 (B.K.), R01CA150153 (B.K.), and P01CA163205 (B.K.) awarded by the National Institutes of Health. The government has certain rights in the invention.

SEQUENCE LISTING

[0003] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Mar. 30, 2018, is named 2935720-7_SL.txt and is 4,791 bytes in size.

TECHNICAL FIELD

[0004] The presently-disclosed subject matter relates to an artificial RNA nanostructure molecule and method to treat brain tumor in a subject. More particularly, the presently disclosed subject matter relates to a RNA nanostructure containing a multiple branched RNA nanoparticle, a brain tumor targeting module, and an effective amount of a therapeutic agent. Further, the presently disclosed subject matter relates to a method of using the RNA nanostructure composition to treat brain tumor in a subject having or at risk of having brain tumor.

INTRODUCTION

[0005] The most common primary brain tumors in adults are glioblastomas, which are also one of the most deadly cancers (1). For glioblastomas, conventional treatment involves surgical resection followed by radiation and concurrent chemotherapy. Even with this treatment regimen, the median survival of patients with glioblastoma is less than 15 months. The poor prognosis is primarily due to tumor recurrence, which is thought to originate from a subset of cancer stem cells that survive the primary treatments. Recent studies suggested that glioblastoma stem cell survived the therapeutic stresses and become more aggressive when they recur, developing resistance to the primary chemotherapy.

[0006] Bacterial virus phi29 DNA packaging RNA (pRNA) molecule is a crucial component in the phi29 DNA packaging motor and contains two functional domains. The intermolecular interaction domain is located at the central region (bases 23-97) and within this domain there are two loops (right hand loop and left hand loop) which are responsible for the hand-in-hand interaction through the four complementary base sequences within these two loops. The other domain is a DNA translocation domain which is located at the 5'/3' paired ends. The right hand loop (bases 45-48) and the left hand loop (bases 82-85) allow for the formation of pRNA dimers, trimers and hexamer rings via intermolecular base-pairing via the interaction of two interlocking loops, the pRNA molecules form dimers, trimers, hexamers, and patterned superstructures [7]. This property of forming self-assembled nanostructure makes pRNA ideal building blocks for bottom-up assembly. RNA nanotechnology has been rapidly growing as a new generation platform for biological and medical application (2-3). As nanotechnology rapidly evolves, many attempts have been made to deliver small interfering RNA (siRNA) using viruses, liposome, lipid, and polymer based nanoparticles (4).

[0007] Clearly there remains a need for improved composition and methods targeting both brain tumor cells and glioblastoma stem cells to treat the primary brain tumor and prevent tumor recurrence is desired. The presently disclosed subject matter relates to RNA nanoparticle containing compositions useful for prophylactic and therapeutic treatment for brain tumors.

SUMMARY

[0008] The presently-disclosed subject matter meets some or all of the above-identified needs, as will become evident to those of ordinary skill in the art after a study of information provided in this document.

[0009] This Summary describes several embodiments of the presently-disclosed subject matter, and in many cases lists variations and permutations of these embodiments. This Summary is merely exemplary of the numerous and varied embodiments. Mention of one or more representative features of a given embodiment is likewise exemplary. Such an embodiment can typically exist with or without the feature (s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this Summary or not. This Summary does not list or suggest all possible combinations of such features.

[0010] In some embodiments, the presently disclosed subject matter provides an artificial RNA nanostructure molecule. The molecule includes a multiple branched RNA junction motif comprising at least one RNA oligonucleotide, and a brain tumor targeting module, and the module is coupled to an RNA junction motif. In some embodiments, the molecule further includes at least one bioactive agent coupled to the RNA junction motif. A non-limiting example of the bioactive agent is a a therapeutic agent. In some embodiments, the RNA oligonucleotide is at least 6 nucleotides in length. In some embodiments, the RNA oligonucleotide includes at least one chemical modification at the 2' position. Non-limiting examples of the chemical modification include 2'Fluoro, 2'Amine, 2'O-Methyl, or a combination thereof.

[0011] In some embodiments, the multiple branched RNA includes a nucleotide sequence 5'-UUG CCA UGU GUA UGU GGG AUC CCG CGG CCA UGG CGG CCG GGA G-3' (SEQ ID NO: 6). In some embodiments, the multiple branched RNA includes a sequence 5'-GATAAGCT CTC CCG GCC GCC ATG GCC GCG GGA T-3' (SEQ ID NO: 7). In some embodiments, the multiple branched RNA junction motif is a three-branched RNA junction motif. In some embodiments, the three-branched RNA junction motif includes a packaging RNA (pRNA) three-way junction